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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,045	10/20/2003	Thomas B. Ottoboni	375430-002t1d1c1	3501

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,045	OTTOBONI ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 10-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/27/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/27/2008 has been entered. The examiner notes the receipt of the amendments and remarks received in the office on 2/27/2008. Claim 9 is canceled. Claims 1-8, 10-16 are pending and are being examined on the merits herein.

Response to Remarks

Applicants' have requested that the provisional double patenting rejection over the claims of '100 application be held in abeyance until such time as claims in the instant application would be otherwise allowable. Hence the rejection of claims 1-8, 10-16 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of copending Application No. 10/977,100 is maintained and is given below for Applicants' convenience. Applicant's arguments regarding 35 U.S.C 103 rejection of claims 1-8, 10-16 under 35 U.S.C. 103(a) as being unpatentable over Bichon et al. (EP 0 458 745) (Also see the corresponding US Patent 5,840,275) in view of Hilmann et al. (US 4,466,442), and further in view of Berstein et al. (WO 91/06287) have been fully considered and the arguments are addressed below. Further search and consideration necessitated the modified and new rejections in this action. The Office Action is made non final.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 10-16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of copending Application No. 10/977,100. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '100 are within the scope of the instant claims and thus anticipate the instantly claimed invention. Specifically, '100 teach compositions comprising microparticles and the herein-claimed excipients (glycine, polyethylene glycol 3350, poloxomer, etc.). '100 teach that the microparticles are comprised of two layers, said layers being comprised of the herein-claimed biodegradable polymers (polylactide) and glutaraldehyde cross-linked albumin. '100 teach that the microparticles have a hollow core filled with nitrogen. The amounts of the components are more explicitly defined in '100 and the scope is thus narrower than for the instantly claimed compositions. Therefore, '100 anticipate the instantly claimed compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8, 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bichon et al. (Applicant-cited reference on IDS: EP 0 458 745) (Also see the corresponding US Patent 5,840,275) in view of Hilmann et al. (US 4,466,442), and further in view of Berstein et al. (Applicant-cited reference on IDS: WO 91/06287).

Bichon et al. teach compositions comprising microparticles filled with air or gas for use in ultrasonic echography (col. 1, lines 1-15; claims 1-3). Bichon et al. teach that the microparticle compositions can be prepared in aqueous solutions or in the solid form (i.e., the isolated cake or powder) for use in echography (col. 1, lines 1-8). Bichon et al. teach that the art recognizes that microparticles used for echography should have diameters in the range of about 0.5 to 10 micrometers (col. 2, lines 26-46). Bichon et al. exemplify a range of polymers useful for forming the membrane coat of the microparticles, including biodegradable polymers such as polylactides, and proteins such as albumin (col. 9, line 2-col. 10, line 8; claim 6). Bichon et al. teach that cross-linking proteins, such as albumin, with glutaraldehyde is an art-recognized method of forming microparticle membrane shells (col. 3, lines 20-53). Bichon et al. teach that the inclusion of sugars, such as sucrose, in order to stabilize the microparticles is known

(col. 2, lines 8-46; col. 8, lines 20-30; col. 10, line 54-col. 11, line 4). Bichon et al. teach the inclusion of surfactants to increase membrane elasticity (claim 11; col. 2, lines 31-46; col. 10, lines 34-46). Bichon et al. also teach the inclusion of "polyethylene glycol of moderate to low M_W" (e.g. PEG 2000)) as membrane-plasticizing agents (col. 10, lines 44-46).

Bichon et al. do not explicitly teach the use of nitrogen as the gas within the core. Bichon et al. do not teach a microparticle with a membrane comprised of two layers of the polymers.

Hilmann et al. teach that nitrogen as a physiologically acceptable gas for incorporation into microparticles for use in echography (claim 14).

Berstein et al. teach the layering of polymers to form microparticles of various size, durability, and release properties. Berstein et al. teach that the microspheres can have layers containing different properties (p. 7, first full paragraph). Berstein et al. teach that the same polymers exemplified by Bichon et al. can be layered to form multilayer microparticles (pp. 13-15). Berstein et al. teach the charge on the proteins can also be modified by crosslinking amino acids to the protein using glutaraldehyde (p 13, lines 9-12). Berstein et al. teach that amino acids are one type of agent than can be included in the microparticles (p. 5, last paragraph). Bernstein teach that protein microspheres can be used in a method other than drug delivery such as to release enzymes, pesticides, fertilizers etc, provide biodegradable non toxic diagnostic agents for use in methods such as radioimaging (p 3, lines 12-14, 19-21).

It would have been obvious to the person of ordinary skill in the art at the time of invention to produce a multilayer microparticle comprising the polymers of Bichon et al., to fill the core of the microparticles with nitrogen.

The person of ordinary skill in the art would have been motivated to layer the polymers of Bichon et al. because Berstein et al. teach that by layering the polymers, the size, durability, and release properties of microspheres can be modulated. The person of ordinary skill in the art would have expected success because Berstein et al. teach that the same polymers exemplified by Bichon et al. can be layered in the preparation of the microparticles.

The person of ordinary skill in the art would have been motivated to use nitrogen as the gas in the core of the particles with a reasonable expectation of success because Bichon et al. teach that the microparticles can be used in echography when a gas is incorporated into the microparticles, and Hilmann et al. teach that nitrogen gas for inclusion in microparticles used for echography.

Claims 1-8, 10-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bichon et al. (Applicant-cited reference on IDS: EP 0 458 745) (Also see the corresponding US Patent 5,840,275) in view of Unger et al. (U.S. 5,846,517).

Bichon et al. teachings discussed as above.

Bichon et al. do not explicitly teach the use of nitrogen as the gas within the core. Bichon et al. do not teach a microparticle with a membrane comprised of two layers of the polymers.

Unger et al. teach a delivery system comprising a contrast agent in vesicle characterized by the presence of one or more walls or membranes and may be formulated from lipids, polymeric materials or proteins and stabilizers including biocompatible polymers. The reference further teach that the vesicles prepared from polymers or proteins may comprise one or more walls or membranes, concentric or otherwise and the walls or membranes of vesicles prepared from lipids, polymers, or proteins may be substantially solid (uniform), or they may be porous or semi-porous. The reference teaches that the vesicles include microbubbles and or microspheres and the internal void may be filled with a liquid or a gas (col. 6, lines 52-67, col. 7, lines 1-15) and further teach nitrogen as a preferred gas (col. 20, line 1). The reference teaches polymeric materials such as polylactic acid, poly d,l lactide co-glycolide polymer (col. 19, lines 26, 31). The reference teaches proteins such as human serum albumin in the vesicle and also teaches chemical alteration of the protein with a difunctional aldehyde, such as glutaraldehyde (col. 47, line 7, col. 48, lines 9-15). The reference teaches that the vesicles can be used for diagnostic and/or therapeutic use (col. 25, lines 15-18). Unger et al. teach polyethylene glycol as a hydrophilic polymer in the vesicle and further teach that molecular weight of 2000 to about 5000 being more preferred (col. 27, lines 55-61). The reference teaches s-glycine as one of the components that can be added in the vesicle composition (col. 49, line 63). In summary, Unger teach microspheres, a vesicle with layering of polymers and also teach nitrogen as a preferred gas to be filled in the internal void.

It would have been obvious to the person of ordinary skill in the art at the time of invention to produce a multilayer microparticle comprising the polymers of Bichon et al., to fill the core of the microparticles with nitrogen.

The person of ordinary skill in the art would have been motivated to layer the polymers of Bichon et al. because of Unger et al.'s teachings. The person of ordinary skill in the art would have expected success because Unger et al. teach that the same polymers exemplified by Bichon et al. can be layered in the preparation of the microparticles.

The person of ordinary skill in the art would have been motivated to use nitrogen as the gas in the core of the particles with a reasonable expectation of success because Bichon et al. teach that the microparticles can be used in echography and Unger et al. teach that the microparticles can be used in diagnostic imaging techniques when a gas is incorporated into the microparticles, and further teach that nitrogen is a preferred gas for inclusion in microparticles used as echogenic vesicles.

Response to Arguments

Applicants' argue that Bichon teaches that the envelope of his microballoon is microporous.and Berstein teaches away from porous microspheres. However, it is deemed that the Berstein reference does not reach the level of a teaching away from porous micropsheres as suggested by Applicant. A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. Berstein in page 29 compares microspheres formed by two

techniques namely water precipitation and solvent separation. The reference states in page 19 “The spheres formed by water precipitation were much more porous and therefore of lower density. In conclusion, the process is not useful for efficient encapsulation...." Bichon does not teach preparing the microspheres applying the same conditions as described by Berstein et al. Hence the microspheres formed by Bichon et al. are not comparable to that of Berstein et al. As Berstein only teaches forming microspheres by water precipitation with the conditions described in the reference is more porous and have disadvantages it does not teach away from the porous microspheres in general. Berstein reference has been added to show layering of polymers in microparticles and layering of polymers modulates size, durability, and release properties of the microparticles. One having ordinary skill in the art would have been motivated to add layers of polymers in microparticles to modulate size, durability and release properties as taught by Berstein.

Applicants’ argue that Bichon teaches microparticles with hollow core and Berstein teach solid microspheres and hence teaches the opposite and therefore legally there can be no reason to combine the Bichon and Berstein references. As stated above, Berstein reference has been used to show that layering of polymers modulate size, durability, and release properties of the microparticles. Hence one having ordinary skill in the art would have been motivated to add layers of polymers in microparticles.

Applicants’ argue that Bichon teach the cross-linking of proteins such as albumin.. and the microspheres are stabilized by denaturation of the membrane" and Berstein teaches the opposite. The applicants’ state from Berstein’s teachings “ that

[m]ost are crosslinked in solution using glutaraldehye, or hardened at elevated temperatures. Unfortunately, there are problems with significant loss of biological activity of incorporated materials and lack of controlled size and in vivo degradation rates". In response, the arguments are not relevant because Berstein's reference teach loss of biological activity of incorporated materials and the instant invention claims other than drugs is incorporated in the microparticles (see claims 15 and 16 of the instant invention). Hence Berstein does not teach away of incorporating agents other than drugs that is claimed in the invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/
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